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Aqueous shunts with mitomycin C versus aqueous shunts alone for glaucoma (Review)

Foo VHX, Htoon HM, Welsbie DS, Perera SA

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Aqueous shunts with mitomycin C versus aqueous shunts alone for glaucoma.
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TABLE OF CONTENTS

[Intervention Review]

Aqueous shunts with mitomycin C versus aqueous shunts alone for glaucoma

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ABSTRACT

Background

Glaucoma affects more than 70 million people worldwide, with about 10% being bilaterally blind, making it the leading cause of irreversible blindness globally. In patients with advanced glaucoma or those who have failed medical treatment without achieving adequate intraocular pressure (IOP) control, trabeculectomy (glaucoma filtration surgery where an ostium is created into the anterior chamber from underneath a partial thickness scleral flap to allow for aqueous flow out of the anterior chamber intointo the subconjunctival space forming a filtering bleb) and aqueous shunt surgery for more complex and refractory cases remain the mainstay therapies. Proliferation of fibrous tissue around an implanted aqueous shunt may block the diffusion of aqueous humour. Mitomycin C (MMC) is one of two commonly used adjunct antifibrotic agents used during aqueous shunt surgery to prevent proliferation of fibrous tissue. However, the effectiveness and safety of the use of intraoperative MMC during aqueous shunt surgery has not been established.

Objectives

To evaluate the effectiveness and safety of MMC versus no MMC used during aqueous shunt surgery for reducing IOP in primary and secondary glaucoma.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2018, Issue 2); Ovid MEDLINE; Embase.com; PubMed; Latin American and Caribbean Health Sciences Literature Database (LILACS); ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We did not use any date or language restrictions in the electronic search for trials. We last searched the electronic databases on 13 February 2018.

Selection criteria

We included randomized controlled trials (RCTs) in which one group of participants received MMC during aqueous shunt surgery and another group did not. We did not exclude studies based on outcomes.

Data collection and analysis

Two review authors independently reviewed titles and abstracts from the literature searches. We obtained full-text reports of potentially relevant studies and assessed them for inclusion. Two review authors independently extracted data related to study characteristics, risk of bias, and outcomes. We used standard methodological procedures expected by Cochrane.

Main results

We included five RCTs, with a total of 333 eyes with glaucoma randomized, and identified two ongoing trials. All included trials examined the effect of MMC versus no MMC when used during aqueous shunt surgery for glaucoma. The trials included participants with different types of uncontrolled glaucoma. One study was conducted in China, one in Saudi Arabia, two in the USA, and one study was a multicenter study conducted in Brazil, Canada, Scotland, and USA. We assessed all trials as having overall unclear risk of bias due to incomplete reporting of study methods and outcomes; two of the five trials were reported only as conference abstracts.

None of the included trials reported mean decrease from baseline in IOP; however, all five trials reported mean IOP at 12 months post-surgery. At 12 months, the effect of MMC on mean IOP compared with no MMC was unclear based on a meta-analysis of trials (mean difference -0.12 mmHg, 95% CI -2.16 to 2.41; low-certainty evidence). Two trial did not report sufficient information to include in meta-analysis, but reported that mean IOP was lower in the MMC group compared with the no MMC group at 12 months.

None of the included trials reported mean change from baseline in visual acuity; however, one trial reported lower mean LogMAR values (better vision) in the MMC group than in the no MMC group at 12 months post-surgery. None of the included studies reported the proportion of participants with stable best-corrected visual acuity. Three trials reported that loss of vision was not significantly different between groups (no data available for meta-analysis).

None of the included studies reported the proportion of participants with a postoperative hypertensive phase, which is defined as IOP > 21 mmHg within 3 months after surgery. Two trials reported adverse events (choroidal effusion, corneal edema, flat anterior chamber, and retinal detachment); however, due to small numbers of events and sample sizes, no clear difference between MMC and placebo groups was observed.

Authors' conclusions

We found insufficient evidence in this review to suggest MMC provides any postoperative benefit for glaucoma patients who undergo aqueous shunt surgery. Data across all five included trials were sparse and the reporting of study methods required to assess bias was inadequate. Future RCTs of this intervention should report methods in sufficient detail to permit assessment of potential bias and estimate target sample sizes based on clinically meaningful effect sizes.

PLAIN LANGUAGE SUMMARY

Aqueous shunt surgery and mitomycin C

What is the aim of this review?
The aim of this Cochrane review was to compare the effects on intraocular pressure (IOP) between participants who received mitomycin C (MMC) during aqueous shunt surgery and participants who did not receive mitomycin C (MMC) during aqueous shunt surgery.

Key messages
We do not know whether MMC helps to lower IOP after aqueous shunt surgery for glaucoma. All the relevant trials that we found were small and they reported little information on how they were conducted. The difference in IOP between the MMC and no MMC group 12 months after surgery was too uncertain to say whether MMC helped to lower IOP.

What was studied in this review?
Glaucoma is a progressive disease in which the optic nerve is damaged. Damage to the optic nerve results in visual impairment and may result in blindness when not properly treated. Increased pressure within the eye, known as intraocular pressure or IOP, is the only known risk factor for glaucoma that can be treated. It is thought that by lowering IOP, damage to the optic nerve will be reduced in eyes with glaucoma. Treatments to reduce IOP include eye drops, laser surgery (trabeculoplasty), trabeculectomy (surgical removal of part of the trabecular meshwork), and aqueous shunt surgery (a small device is implanted in the eye to help drain fluid to reduce pressure). Aqueous shunt surgery usually is performed in eyes for which eye drops and laser surgery have not reduced IOP.

Sometimes medications, such as MMC, are used alongside aqueous shunt surgery. These types of medications, known as antifibrotic agents, are used to prevent tissue growth around the implanted device which may block the fluid from draining from the eye. However, it is unknown whether these types of medications are effective and whether there are any unwanted adverse effects. The purpose of this review was to evaluate the effectiveness and safety of MMC when used during aqueous shunt surgery.

What are the main results of the review?
We included five studies with a total of 333 eyes with glaucoma. All five trials reported few details about how they were designed and carried out and few outcomes regarding IOP. Thus, we do not know whether MMC was advantageous compared with placebo. We found no clear benefit or harm for MMC versus no MMC during aqueous shunt surgery.

How up-to-date is this review?
Cochrane researchers searched for studies that had been published up to 13 February 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Aqueous shunts with versus without mitomycin C for glaucoma

Aqueous shunts with versus without mitomycin C (MMC) for glaucoma

Population: adults with glaucoma requiring aqueous shunt surgery

Settings: ophthalmology clinics

Intervention: MMC used during aqueous shunt surgery

Comparison: placebo (balanced salt solution)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	MMC				
Mean IOP (mmHg) *Follow-up: 12 months*	Mean IOP ranged from 15.3 to 16.8 mmHg	The effect of MMC on mean IOP compared with no MMC was unclear based on a meta-analysis of trials (mean difference -0.12 mmHg, 95% CI -2.16 to 2.41)	-	78 (3)	⊕⊕⊖⊖ **low[1,2]**	Two additional studies reported that mean IOP was lower in the MMC group compared with the placebo group.
Control of IOP, assessed as the mean decrease in IOP from baseline *Follow-up: 12 months*	See comment	-	-	-	-	None of the included studies reported this outcome.
Mean change from baseline in visual acuity *Follow-up: 12 months*	See comment	-	-	-	-	One trial reported lower mean LogMAR values in the MMC group than in the placebo group. Lower LogMAR values represent better visual acuity.

Proportion of participants with stable best-corrected visual acuity *Follow-up: 12 months*	See comment	-	-	-	-	None of the included studies reported this outcome.
Proportion of participants with decreased visual acuity *Follow-up: 12 months*	See comment	-	-	-	-	Three trials reported that loss of vision was not significantly different between groups (no data available for meta-analysis).
Proportion of participants with a postoperative hypertensive phase *Follow-up: within 24 hours of surgery*	See comment	-	-	-	-	None of the included studies reported this outcome.
Proportion of participants with an adverse event *Follow-up: 12 months*	See comment	-	-	85 (2)	⊕⊕⊖⊖ **low**[1, 2]	Two studies reported four adverse events (choroidal effusion, corneal edema, flat anterior chamber, and retinal detachment). Due to small numbers of events and sample sizes, no clear difference between MMC and placebo groups was observed.

CI: confidence interval; **RR:** risk ratio; **MMC:** mitomycin C; **mmHg:** millimeter of mercury; **IOP:** intraocular pressure

*The basis for the **assumed risk** is the mean risk in the placebo group across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the placebo group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1]Downgraded for unclear or high risk of bias among included trials
[2]Downgraded for imprecision (wide confidence intervals)

BACKGROUND

Description of the condition

Glaucoma is a group of optic neuropathies characterized by the degeneration of retinal ganglion cells, which lead to cupping of the optic disc and visual loss (Weinreb 2004). Glaucoma affects more than 70 million people worldwide, with about 10% being bilaterally blind (Quigley 2006), making it the leading cause of irreversible blindness globally. Reduction of intraocular pressure (IOP) is the only proven, modifiable method to prevent development and slow the disease's progression (Kass 2002). Thus, treatment of glaucoma generally starts when IOP is greater than 25 mmHg, even without signs of early damage to the optic nerve. The initial treatment may be eye drops or laser trabeculoplasty. Traditionally, trabeculectomy is the gold standard glaucoma procedure used after topical medical treatment has been deemed ineffective. Aqueous shunts have been used primarily for more complex and refractory glaucomas cases, such as for patients with advanced uveitic or neovascular glaucoma, or for those with extensive conjunctival scarring due to multiple failed trabeculectomies or other causes.

Description of the intervention

The term aqueous shunt is preferred by the American National Standards Institute (ANSI) as most appropriate for the group of devices referred to in current peer-reviewed literature as glaucoma drainage devices, tube implants, or inappropriately as setons, a term that should be reserved for non-lumened devices (ANSI Z80.27 2001; Minckler 1997). Aqueous shunts are constructed from materials (polypropylene or silicone rubber) to which fibroblasts cannot adhere tightly in order to create a space into which aqueous humor can drain via a connecting tube when implanted. The Ahmed, Baerveldt,, and Molteno devices are the most commonly used aqueous shunts today, while other devices, such as the OptiMed, White shunt pump, Joseph implant, and Krupin valve have fallen out of use. Few details are available regarding the specifications of the Hunan shunt (Duan 2003). The various devices differ depending on explant surface areas, shape, plate thickness, presence or absence of a valve, and details of surgical installation (Minckler 2008).

Ab-interno procedures not requiring scleral dissection, such as trabectome or implantation of the iStent (Glaukos, Laguna Hills, CA), are not covered in this review. Devices such as the Ex-PRESS shunt, OloGen implant, SKgel implant,, and T-flux implant, which are used to enhance outflow or to modify healing and promote continued drainage from the anterior chamber following a standard trabeculectomy (scleral dissection), are not considered aqueous shunts for the purposes of this review; these devices are covered in a separate Cochrane review (Wang 2013). Likewise, we have not addressed current exploration of aqueous drainage into the suprachoroidal space such as with the gold shunt (Solex, Inc., Boston, MA).

Mitomycin C (MMC) is an adjunct anti-metabolite than can be applied during aqueous shunt surgery to prevent the conjunctiva and Tenon's capsule from scarring onto the scleral flap. After the creation of a fornix-based conjunctival flap during surgery, a large Weck-cell sponge soaked in a 0.1 to 0.5 mg/mL solution of MMC usually is placed on the episclera under the conjunctiva and Tenon's capsule at the site where the implant plate of the aqueous shunt is to be placed. There is a contact time of five minutes, before the anterior edge of the plate is secured to the sclera. However, there are variations in the technique used to deliver MMC, such as the use of different dosages of MMC, application of more than one sponge, subconjunctival injection of MMC, increased or decreased contact time, or a combination of these.

How the intervention might work

Aqueous shunts control IOP in glaucoma management by creating an alternate pathway for aqueous humor to leave the anterior chamber of the eye, for example, by means of translimbal or transcleral drainage. Four to six weeks after surgery, a fibrous capsule forms around the posterior episcleral plate, providing resistance to aqueous flow (Rosenberg 1996). Aqueous humor moves through the capsule into surrounding tissues by passive diffusion and is removed from the periocular space by venous capillaries or lymphatics (Minckler 1987; Prata 1995; Schocket 1986; Wilcox 1994). The results of the Trabeculectomy versus Tube (TVT) study confirmed that using tube-shunt surgery after the first trabeculectomy is a good alternative to a second trabeculectomy. Patients so treated more often had adequate and sustained IOP reduction in the long term.

Long-term IOP reduction after implant surgery depends on the resistance of the aqueous flow across the bleb wall, which in turn depends on the thickness and density of the bleb's capsule. A thin bleb is more permeable than a thick one, allowing more aqueous humor to filter out with a subsequent greater reduction of IOP. Excessive scarring with blockage of the posterior aqueous flow is the most common cause of late failure of the Molteno tube-shunt procedure, causing success rates with the aqueous shunts to decrease over time after surgery (Rosenberg 1996).

MMC is an alkylating agent that inhibits DNA-dependent RNA synthesis and has been shown to prevent fibroblast proliferation (Khaw 1992; Singh 1988). When applied between the sclera and Tenon's capsule before placement of the plate, MMC inhibits fibroblastic proliferation and results in relatively avascular filtration blebs with less fibrovascular scarring and prolonged bleb function. In keeping with the proven efficacy of MMC with trabeculectomy (Wilkins 2010), many surgeons use antifibrotic agents as adjunctive treatment during aqueous shunt surgery. A recent Cochrane review concluded that regular-dose postoperative 5-Fluorouracil (5-FU) injections are only beneficial to eyes at high risk of failure and those undergoing primary trabeculectomy, with no good evidence for their routine use in combined cataract extraction and trabeculectomy (Green 2014). The use of 5-FU largely has been superceded by the newer intraoperative MMC.

However, studies on MMC use have shown discordant results. Investigators of some studies have concluded that MMC is beneficial for improving success rates in aqueous shunt surgeries, for example by contributing to better IOP-lowering outcomes. Perkins 1995 found that 76% of participants with the single-plate Molteno aqueous shunt, and 68% with the double-plate Molteno aqueous shunt, had an IOP of 21 mmHg or less after 9 months versus 17% in the control group at one year. Azuara-Blanco 1997 also reported a 73% success rate with Baerveldt implantation and MMC after one year of follow-up in eyes with complicated glaucoma. Hence, adjunct MMC was observed to improve outcomes in high-risk filtering surgery. However, due to different dosages, application times, and patient populations, exact comparisons of

these studies become difficult, though there appears to be a trend towards lower IOP over a longer period of time postsurgery when MMC is used.

Conversely, investigators of other studies have found that MMC did not increase the short- or intermediate-term success rates of valved and non-valved aqueous shunts to the same extent. The majority of previous studies suggested intraoperative MMC during the implantation of non-valved aqueous shunts was not effective in increasing the success rates of this procedure, unlike with valved devices, which allow the contact of aqueous humor with the subconjunctival space from postoperative day one and may lead to a different result. Costa 2004 reported no benefit from adjunctive MMC during the implantation of the Ahmed aqueous shunt, although the study was underpowered to detect small differences in outcomes between groups. Nor did Lee 1997 detect significant differences in success rates between MMC and control groups after five years in subjects who underwent 1-stage, single-plate Molteno implantation with adjunct intraoperative MMC. Trible 1997 failed to conclude that MMC benefited patients undergoing Baerveldt 350 mm^2. Similarly, Cantor 1998 did not find any significant differences in outcomes between Molteno implants supplemented with MMC and the control group, and Kook 2000 reported success rates of 80% and 77% at one and two years, respectively, when MMC was used during Ahmed glaucoma valve implantation.

The efficacious dose range of MMC in aqueous filtration procedures is unknown, although it is speculated that a higher dose of MMC or longer exposure time provides better fibrosis control as well as lowers IOP, as shown in eyes undergoing primary trabeculectomy (Robin 1997). These results may not be applicable to those who have undergone previous intraocular surgery. A precise drug delivery device would be needed to elucidate the lowest and most efficacious dose for high-risk patients undergoing aqueous shunt surgery.

Finally, potential side effects of MMC may discourage its use. Early complications commonly include a flat anterior chamber and hypotony (IOP $\leq$ 6 mmHg); hypotony is more frequent in aqueous shunts used with MMC due to the drug's possible effect on aqueous production (Meitz 1995). Late complications include persistent hypotony, need for plate revision, eye phthisis/no light perception, cataract requiring extraction, persistent inflammation, persistent suprachoroidal hemorrhage/choroidals, need for corneal transplant, retinal detachment, vitreous hemorrhage, aqueous misdirection, and conjunctival/wound leak.

Why it is important to do this review

There has been no recent systematic review of randomized trials to summarize the totality of the evidence of the effectiveness and safety of intraoperative mitomycin C in aqueous shunt surgery for glaucoma. A Cochrane review of aqueous shunts for glaucoma was published in 2017 (Tseng 2017), but that review did not evaluate the use of MMC in aqueous shunt procedures. In another systematic review, Minckler 2008 found no evidence of a beneficial effect of antifibrotic agents as adjuncts to aqueous shunt procedures. Also, an earlier Cochrane review published in 2005 on 'Motomycin C in glaucoma surgery' did not include the use of MMC in aqueous shunt surgery, but mainly in trabeculectomy and combined trabeculectomy and cataract extraction. However, larger numbers of advanced glaucoma eyes in the last few decades have required vision-sustaining therapies beyond traditional medical and surgical treatments. Thus, there is a need for regular updates of general information on aqueous shunt surgery and strategies to improve its success rate.

OBJECTIVES

To evaluate the effectiveness and safety of MMC versus no MMC used during aqueous shunt surgery for reducing IOP in primary and secondary glaucoma.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) which compared the use of MMC versus no MMC during aqueous shunt surgery for glaucoma.

Types of participants

We included trials in which participants had been diagnosed with glaucoma in at least one eye, irrespective of the lens status. There were no restrictions with regard to age, gender, ethnicity, comorbidities among participants, or the number of trial participants. We included trials that had enrolled participants undergoing aqueous shunt insertion alone or in combination with other types of ocular surgery (e.g. cataract surgery) and those who may have had previous ocular surgery.

Types of interventions

We included trials of aqueous shunt surgery that compared the use with the non-use of adjunctive MMC. We included trials irrespective of the type of aqueous shunt used.

Types of outcome measures

Primary outcomes

The primary outcome was control of IOP, assessed as the mean decrease from baseline (preoperative IOP) to 12 months, measured using Goldmann tonometry, Tonopen, or another standard device.

Secondary outcomes

1. Mean IOP at 12 months, measured using Goldmann tonometry, Tonopen, or another standard device.
2. Mean change from baseline in visual acuity at 12 months, measured using the chart developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) or equivalent.
3. The proportion of participants with stable best-corrected visual acuity at 12 months. We considered visual acuity to be stable when unchanged or within one line of letters of baseline measurement on the visual acuity chart used (Snellen, ETDRS, logMAR).
4. The proportion of participants with decreased visual acuity at 12 months, defined as loss of two or more lines (10 or more letters on a LogMAR chart) compared with baseline using the same measurement methods. We documented reasons for vision loss, when reported.
5. The proportion of participants with a postoperative hypertensive phase (IOP > 21 mmHg) within 3 months after surgery.

6. Visual field at 12 months as measured by any method and reported as means, proportions, or categorically (e.g. visual field worsening, unchanged, improved).
7. Total number of anti-glaucoma medications, both topical and systemic, as adjuncts to surgery taken at different times during follow-up.

We also considered secondary time points for all outcomes at weeks 1 to 12, 6 months, and as available throughout follow-up after 12 months.

Adverse outcomes

We compared complications and adverse events between treatment groups that occurred throughout follow-up in each trial. Complications included those from aqueous shunts, use of MMC, or both.

Follow-up

We placed no restriction on the duration of follow-up, but the primary analysis of outcomes was 12 months after surgery.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for randomised controlled trials and controlled clinical trials. There were no language or publication year restrictions. The electronic databases were last searched on 13 February 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 2) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 13 February 2018) (Appendix 1).
- MEDLINE Ovid (1946 to 13 February 2018) (Appendix 2).
- Embase.com (1947 to 13 February 2018) (Appendix 3).
- PubMed (1948 to 13 February 2018) (Appendix 4).
- Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to 13 February 2018) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 13 February 2018) (Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 13 February 2018) (Appendix 7).

Searching other resources

We searched the reference lists of reports from trials we identified to look for additional trials. We did not conduct manual searches of conference proceedings or abstracts specifically for this review. We used the Science Citation Index to find studies that cited the identified trials (last searched 7 April 2018).

Data collection and analysis

Selection of studies

Two authors independently assessed the titles and abstracts of all records identified by the electronic and manual searches. We classified each record as 'definitely relevant', 'possibly relevant', or 'definitely not relevant'. We obtained full-text reports of records classified as 'definitely relevant' or 'possibly relevant'. We classified each full-text report as 'included', 'awaiting assessment', or 'excluded'. A third author resolved any disagreements in full-text assessment. For studies written in languages not read by authors, we used Google Translate or requested translation of the full-text report in order to determine eligibility. We contacted the primary investigators to clarify eligibility of studies classified as 'awaiting assessment'. We allowed two weeks for investigators to respond; when no response was received, we assessed the eligibility of the study based on the available information. All studies that met the inclusion criteria underwent data extraction and assessment for risk of bias. We documented the reasons for excluding studies identified by both authors as 'excluded'. The authors were unmasked to the report authors, institutions, and trial results during these assessments.

Data extraction and management

Two authors independently extracted data for study design and methods, participant characteristics, and primary and secondary outcomes onto paper data collection forms developed in collaboration with Cochrane Eyes and Vision. The forms were first piloted on two trials, and then subsequently revised to be used to extract data from all included trials. We resolved discrepancies through discussion. We contacted primary investigators for missing data. We allowed two weeks for investigators to respond; when no response was received, we extracted data based on the available information. One author entered data into Review Manager 5 (RevMan 5) (Review Manager 2014), and a second review author verified the data entered.

Assessment of risk of bias in included studies

Two authors assessed trials for potential risk of bias according to methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We considered the following domains: method of sequence generation and concealment of allocation before randomization (selection bias), masking of investigators and participants (performance bias), masking of outcome assessors (detection bias), rates of follow-up and intention-to-treat analysis (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias, such as funding sources. Two authors independently judged each study with respect to each risk of bias parameter as being at low risk, unclear risk, or high risk. We contacted primary investigators when study methods were unclear. We allowed two weeks for investigators to respond; when no response was received, we assessed risk of bias based on the available information. A third author resolved any disagreements.

Measures of treatment effect

We calculated mean differences with 95% confidence intervals (CIs) for continuous outcomes: control of IOP (mean decrease from baseline in IOP), mean IOP, mean change from baseline in visual acuity, and total number of antiglaucoma medications.

We calculated the risk ratio with 95% CIs for dichotomous outcomes: proportion of participants with stable best-corrected visual acuity, proportion of participants with decreased visual acuity, proportion of participants with a postoperative hypertensive phase, and proportion of participants with an adverse event.

We planned to include visual field data reported as means, proportions, or categorically and analyze according to the type of data; however, no study reported visual field outcomes.

Unit of analysis issues

The unit of analysis was the individual with one study eye per person. One trial (Duan 2003) included five participants where both eyes were included. It is unclear whether analysis accounted for the non-independence of these eyes.

Dealing with missing data

In instances of missing or unclearly reported data, we attempted to contact primary study investigators for supplemental information to clarify reported results. We allowed two weeks for investigators to respond; however, we received no additional information as most studies were published more than 20 years ago. We did not impute data for the purposes of this review.

Assessment of heterogeneity

We assessed methodological, clinical, and statistical heterogeneity. To assess methodological and clinical heterogeneity, we examined and compared measures within in each trial such as participant characteristics, inclusion/exclusion criteria, and assessments of included outcomes. To assess statistical heterogeneity, we examined the I^2 statistic when data were sufficient for meta-analysis,. We considered a value larger than 60% to indicate substantial statistical heterogeneity. We also examined the Chi^2 test results and degree of overlap of confidence intervals, which would suggest statistical heterogeneity.

Assessment of reporting biases

We did not assess reporting bias with funnel plots because there were fewer than 10 studies included in the meta-analysis. If future updates to this review include 10 or more studies in any meta-analysis, we intend to use funnel plots to examine small study effects. We assessed selective outcome reporting as part of the study-level 'risk of bias' assessment.

Data synthesis

We combined data in meta-analysis when there was no clinical or methodological heterogeneity detected and when data were sufficiently reported. We used the fixed-effect model because all meta-analyses included three or fewer trials. In the event of heterogeneity of the studies and paucity of included studies, meta-analysis would not be carried out. Individual results for each comparison would be reported.

Subgroup analysis and investigation of heterogeneity

Due to an insufficient number of studies in each meta-analysis, we decided against performing any subgroup analyses. If future updates include more studies, we will reassess whether subgroup analyses should be performed.

Sensitivity analysis

We did not conduct sensitivity analysis for this review due to insufficient data. We will reassess these analyses in future updates.

Summary of findings

We assessed the certainty of evidence for each outcome using the GRADE methodology (GRADEpro 2015). GRADE uses the following criteria to assess the evidence: risk of bias, indirectness, inconsistency, imprecision, and publication bias. Two review authors independently assessed each outcome for certainty as very low, low, moderate, or high. Disagreements were resolved by discussion. The main findings of the GRADE assessments for each outcome are summarized in a 'Summary of findings' table. The following seven prespecified outcomes were included in the table:

1. Control of IOP, assessed as the mean decrease from baseline (preoperative IOP) to 12 months, measured using Goldmann tonometry, Tonopen, or another standard device.
2. Mean IOP at 12 months, measured using Goldmann tonometry, Tonopen, or another standard device.
3. Mean change from baseline in visual acuity at 12 months, measured using the chart developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) or equivalent.
4. The proportion of participants with stable best-corrected visual acuity at 12 months. We considered visual acuity to be stable when unchanged or within one line of letters of baseline measurement on the visual acuity chart used (Snellen, ETDRS, logMAR).
5. The proportion of participants with decreased visual acuity at 12 months, defined as loss of two or more lines (10 or more letters on a LogMAR chart) compared with baseline using the same measuring methods. We documented reasons for vision loss when reported.
6. The proportion of participants with a postoperative hypertensive phase (IOP > 21 mmHg) within 3 months after surgery.
7. The proportion of participants with an adverse event.

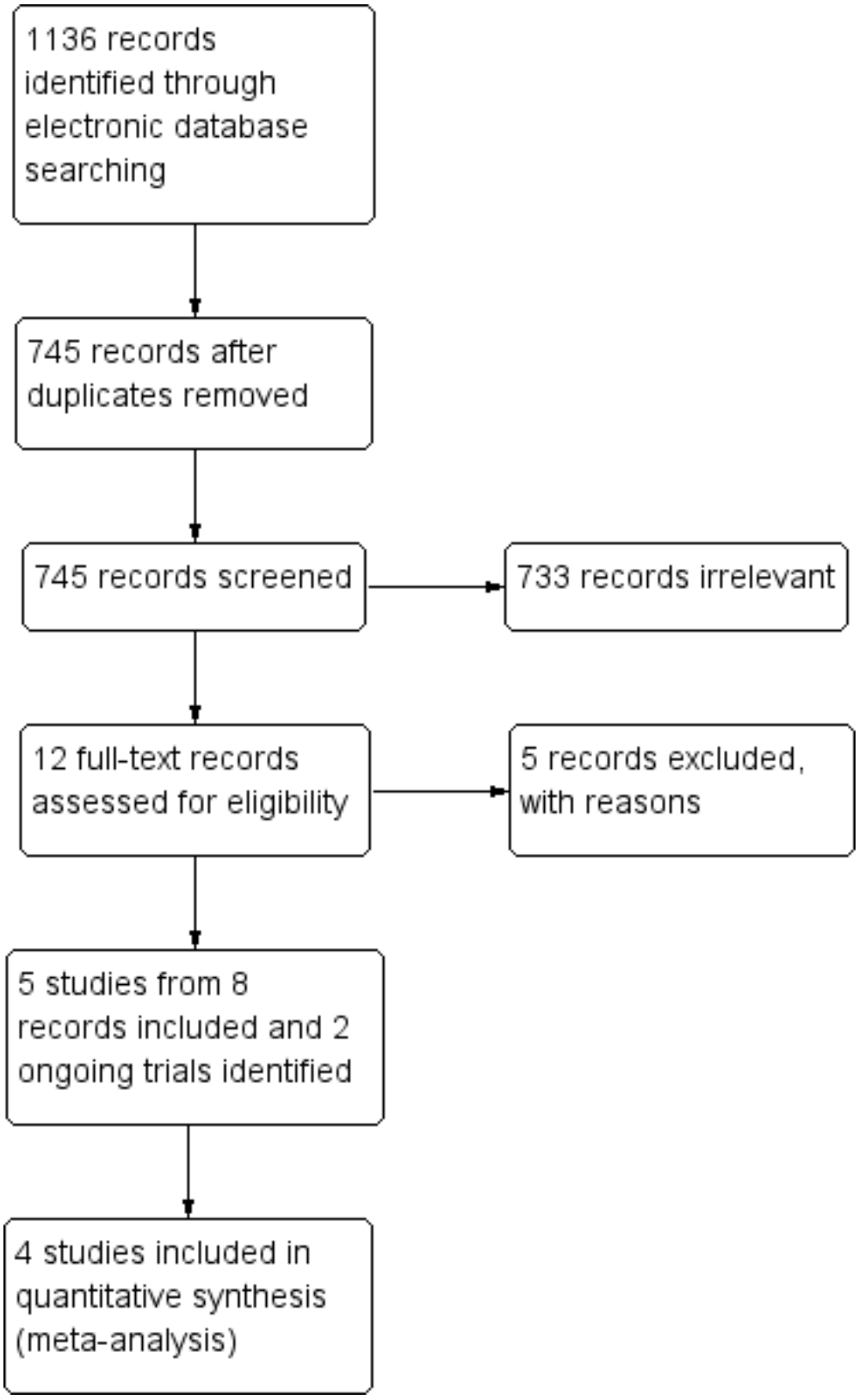
RESULTS

Description of studies

Results of the search

The electronic search performed on 13 February 2018 resulted in 745 unique records (Figure 1). Of these 745 records, we classified 15 as possibly relevant and reviewed the full-text reports. From the 15 reports, we excluded five studies, included five studies from eight records (Cantor 1998; Costa 2004; Duan 2003; Kalenak 1996; Sayyad 1995), and identified two ongoing studies (see Characteristics of ongoing studies). We identified no additional studies upon searching other sources.

Figure 1. Study flow diagram.



Included studies

We included five RCTs with a total of 333 eyes with glaucoma in our review. All trials compared the use of intraoperative MMC versus no intraoperative MMC during aqueous shunt surgery for reducing IOP in primary and secondary glaucoma. Two trials were reported only as conference abstracts presented more than 20 years ago, thus information from these trials was limited (Kalenak 1996; Sayyad 1995). We provide study characteristics of individual studies in the Characteristics of included studies table.

Types of participants

All five trials included participants with uncontrolled primary or secondary glaucoma. Cantor 1998 excluded participants with previous aqueous shunt surgery; Kalenak 1996 included participants who had at least one previous glaucoma filtering operation. The remaining three studies did not report eligibility criteria based on previous glaucoma surgery; however, all five trials included only participants for whom IOP was uncontrolled with standard treatment. Of the three studies that reported the mean ages of participants, the range was 50 to 67 years. One study was conducted in China (Duan 2003), one in Saudi Arabia (Sayyad 1995), and two in the USA (Cantor 1998; Kalenak 1996) were all single centre studies; one study was a multicenter study conducted in Brazil, Canada, Scotland, and USA with study participants under the care of surgeons from four centres (though the number of surgeons was not specified in the study) (Costa 2004). Only Cantor 1998 specifically mentioned that all study participants were under the care of a single surgeon; this information was not specified in the rest of the studies.

Types of interventions

All trials compared intraoperative MMC versus placebo (balanced salt solution) during aqueous shunt surgery. Three studies used the Molteno implant: Cantor 1998 used the pressure-ridge, double-plate implant; Kalenak 1996 and Sayyad 1995 used the single-plate implant. Costa 2004 examined the effect of MMC use in conjunction with Ahmed Glaucoma Valve implant and Duan 2003 used the Hunan aqueous drainage implant. The concentration of MMC solution ranged from 0.2 to 0.5 mg/mL and was applied for 1 to 5 minutes across studies.

Types of outcomes

All five trials measured IOP; however, none of the trials reported mean IOP change from baseline which was the primary outcome for this review. Rather, all the trials reported mean IOP at a time point as an outcome. Three trials also reported the proportion of participants with surgical success (Costa 2004; Duan 2003; Kalenak 1996), defined as 1) IOP between 6 and 21 mmHg or 2) IOP reduction of at least 30% relative to baseline.

Three trials measured visual acuity; however, none of these trials reported visual acuity outcomes as defined in this review (mean change from baseline, proportion with stable vision, and proportion with loss of two or more lines of vision). Cantor 1998 reported mean LogMAR visual acuity (converted from a Snellen chart) at a time point. Costa 2004 and Duan 2003 reported the proportion of participants with decreased visual acuity, but what they considered a decrease in visual acuity was not defined.

Two trials collected data on the number of antiglaucoma medications and reported the mean number of medications used in each group (Cantor 1998; Costa 2004). These same two studies reported adverse outcomes, such as choroidal effusion, flat anterior chamber, corneal edema, and retinal detachment. No other study reported adverse events. No trial reported outcomes related to the postoperative hypertensive phase or visual field.

Follow-up times varied between studies, ranging from at least 6 months in Kalenak 1996 to 72 months in Duan 2003. Cantor 1998 and Sayyad 1995 recorded a maximum follow-up time of 12 months. Costa 2004 followed participants for 18 months.

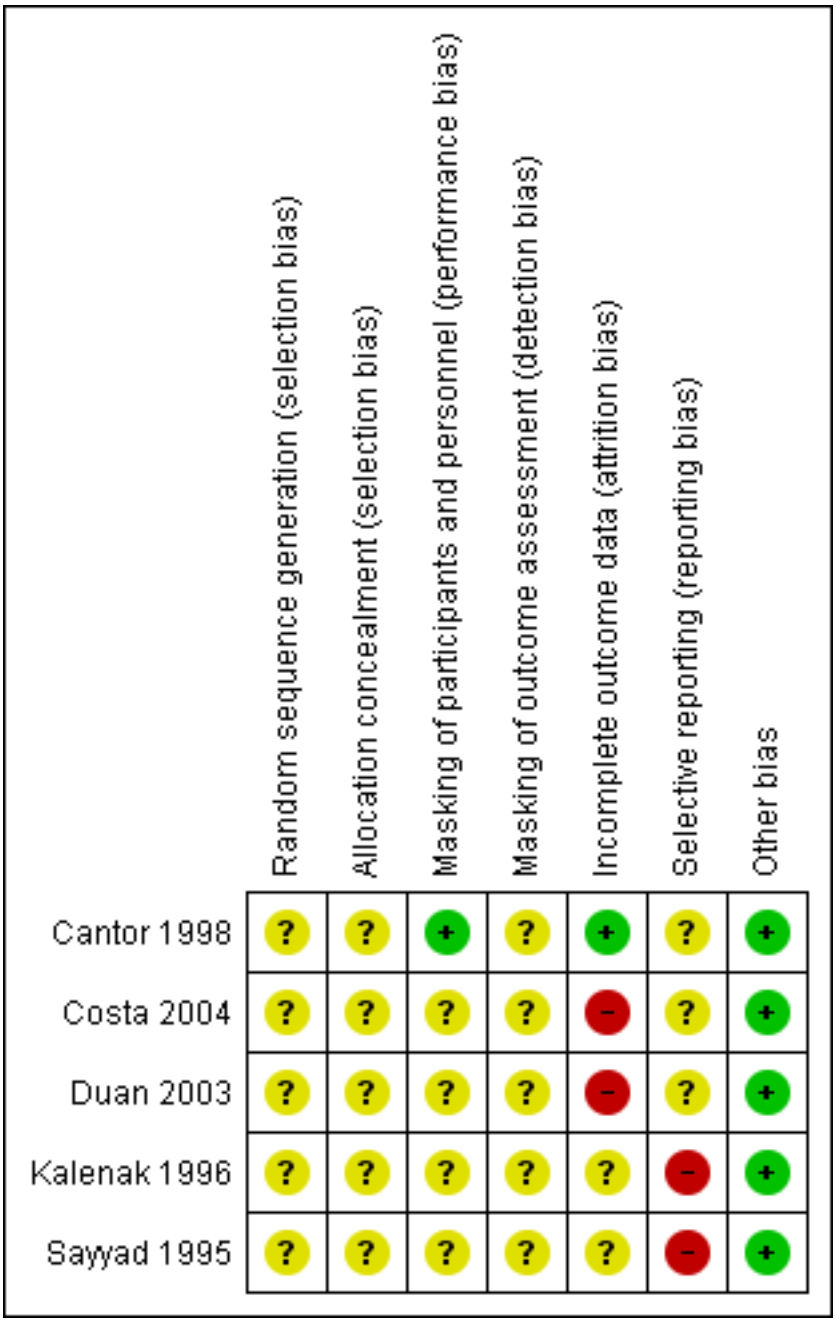
Excluded studies

We excluded five studies from the review following the full-text assessment of reports. Reasons for exclusion are provided in the Characteristics of excluded studies table. Briefly, we excluded three studies due to ineligible interventions and two studies that were not randomized.

Risk of bias in included studies

A summary of risk of bias assessment for each trial is shown in Figure 2.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

None of the five included trials reported methods of randomization or allocation concealment. We assessed the risk of bias for these domains to be unclear for all five trials.

Masking (performance bias and detection bias)

Although all trials used a control (balanced salt solution) group, only Cantor 1998 specifically mentioned masking participants and personnel. We assessed Cantor 1998 as at low risk and the other four trials as at unclear risk of performance bias. Also, only Cantor 1998 mentioned staining balanced salt solution with gentian violet in order to match the purple colour of MMC.

None of the included trials mentioned masking of outcome assessment; thus, we assessed all studies as at unclear risk of detection bias.

Incomplete outcome data

We assessed Cantor 1998 to have a low risk of attrition bias as all participants had complete data at six months and 84% had complete data at 12 months of follow-up. We assessed two trials, Costa 2004 and Duan 2003, to have a high risk of attrition bias due to incomplete data for 47% and 25% of participants, respectively, at 12 months of follow-up. Kalenak 1996 and Sayyad 1995, which were reported only as conference abstracts, did not provide sufficient

information to assess incomplete outcome data; thus, we assessed both studies as at unclear risk of attrition bias.

Selective reporting

We assessed the three included studies with full-text reports as having unclear risk of reporting bias because no protocol was available for these trials to compare planned outcomes versus reported outcomes (Cantor 1998; Costa 2004; Duan 2003). We assessed the two studies reported only as conference abstracts at high risk of reporting bias because no full-length report was available more than 20 years after the trials were presented at a conference (Kalenak 1996; Sayyad 1995).

Other potential sources of bias

We identified no other potential sources of bias. The trials were conducted before prospective trial registration was required and no trial reported industry funding.

Effects of interventions

See: **Summary of findings for the main comparison** Aqueous shunts with versus without mitomycin C for glaucoma

Aqueous shunts with versus without mitomycin C (MMC) for glaucoma

A summary of main outcomes is provided in Summary of findings for the main comparison We defined the primary time point to assess the effects of MMC at 12 months after aqueous shunt surgery. Outcomes at predefined secondary time points (1 to 12 weeks, 6 months, and as available throughout follow-up after 12 months) were reported also, when available from included studies.

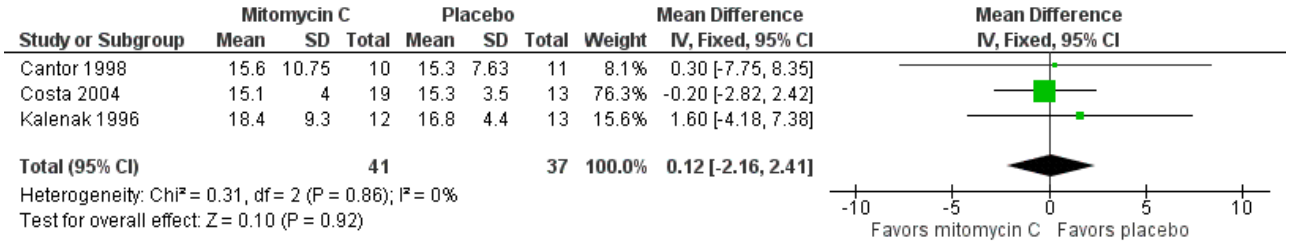
Control of intraocular pressure

We defined control of intraocular pressure (IOP) as a mean decrease from baseline in IOP. None of the included trials reported this outcome.

Mean intraocular pressure

Mean IOP was the primary outcome in all five included studies. At 12 months, the effect of MMC on mean IOP compared with no MMC was unclear in three trials (mean difference (MD) 0.12, 95% CI -2.16 to 2.41; Figure 3). Sayyad 1995 did not report sufficient information for inclusion in the comparison, but reported that mean IOP was lower in the MMC group (mean = 14.9 mmHg, standard deviation (SD) = 5.3 mmHg) compared with the no MMC group (mean = 18.3 mmHg, SD = 4.4 mmHg) at 12 months. We did not include Duan 2003 in the meta-analysis because the number of participants (or eyes) associated with one year results was not clearly reported. Further, the authors did not specify how they managed correlation between units of analyses.

Figure 3. Forest plot of comparison: 1 Mitomycin C versus placebo during aqueous shunt surgery, outcome: 1.4 Mean intraocular pressure at 12 months.



We graded the certainty of evidence for mean IOP at 12 months as low, downgrading for potential risk of bias within trials and imprecision.

Three trials evaluated mean IOP at other time points. Sayyad 1995 reported that MMC "may provide early postoperative IOP control" at 2 weeks and 12 weeks post-operation based on the mean IOP of groups at each time point. Cantor 1998 and Costa 2004 reported unclear effects in mean IOP at 4 weeks (MD -2.54 mmHg, 95% CI -6.64 to 1.55), 12 weeks (MD 1.83 mmHg, 95% CI -1.91 to 5.58), and 6 months (MD 0.28 mmHg, 95% CI -2.45, 3.00) post-operation. We graded the certainty of evidence for mean IOP at these time points as low, downgrading for potential risk of bias within trials and imprecision.

Mean change in visual acuity

None of the included trials reported this outcome, which was defined as the mean change in visual acuity. One trial instead reported mean visual acuity at 12 months to be 1.5 (standard error 0.4) LogMAR in the MMC group (n = 10) and 2.1 (standard error 0.5) LogMAR in the placebo group (n = 11). Higher LogMAR values represent worse vision.

Loss of vision

Loss of vision was defined as a loss of two or more lines (10 or more letters on a LogMAR chart) compared with baseline. No trial reported this outcome as defined in this review; however, three trials reported some information on loss of vision.

Cantor 1998 reported that both groups experienced a significant loss of vision at the 12-month time point. Costa 2004 did not report any specific values or time points regarding visual acuity, simply stating that three eyes (9%) in the MMC group and four eyes (15%) in the control group had clinically significant reductions in best-corrected visual acuity. At 36 months, Duan 2003 reported the proportion of participants with decreased best-corrected visual acuity to be 3/15 participants in the MMC group and 5/31 participants in the control group. None of the other included trials reported this outcome at any time point.

Hypertensive phase

We defined the postoperative hypertensive phase as IOP > 21 mmHg within 3 months after surgery. None of the included trials reported this outcome.

Total number of antiglaucoma medications

While none of the included trials reported the number of antiglaucoma medications, two trials calculated the mean number of medications used in each group at 12 months (Cantor 1998; Costa 2004). There was no clinically significant difference between groups as the difference was within one medication (mean difference -0.13, 95% CI -0.60 to 0.35; Analysis 1.5). We graded the certainty of evidence for number of antiglaucoma medications as moderate, downgrading for potential risk of bias within trials.

Adverse outcomes

Two studies reported adverse events (Cantor 1998; Costa 2004). Both studies reported four of the same adverse events; however, due to small numbers of events and sample sizes, no clear difference between MMC and placebo groups was observed.

- choroidal effusion (risk ratio (RR) 0.73, 95% CI 0.28 to 1.87)
- corneal edema (RR 2.21, 95% CI 0.63 to 7.75)
- flat anterior chamber (RR 1.45, 95% CI 0.48 to 4.41)
- retinal detachment (RR 1.50, 95% CI 0.22 to 10.31)

We graded the certainty of evidence for adverse events as low, downgrading for potential risk of bias within trials and imprecision.

DISCUSSION

Summary of main results

Despite a comprehensive literature search to evaluate the impact of intraoperative MMC during aqueous shunt surgery compared with aqueous shunt surgery without MMC, only five RCTs with few outcomes met the inclusion criteria (Cantor 1998; Costa 2004; Duan 2003; Kalenak 1996; Sayyad 1995). Three types of aqueous shunts were used among the trials (Ahmed, Hunan, Molteno), but the methodologies were similar enough to directly compare results when data were sufficient for meta-analysis.

No trial reported the primary outcome for this review, mean decrease from baseline in IOP at 12 months. Of the four trials included in meta-analysis of mean IOP at 12 months, the effect of MMC compared with placebo was unclear due to unknown risks of bias in the trials and the imprecision of the effect estimate. Data were too sparse to assess the effect of MMC compared with placebo for all other review outcomes (visual acuity, postoperative hypertensive phase, visual field, number of antiglaucoma medications used postoperatively). Adverse events reported by two studies included choroidal effusion, flat anterior chamber, corneal edema, and retinal detachment.

Overall completeness and applicability of evidence

All five trials had wide variability in terms of the participants' conditions at baseline, though the proportion of participants with the respective subtypes of glaucoma were similar between treatment groups. Participants presented with neovascular glaucoma, aphakic glaucoma, primary angle closure glaucoma, primary open angle glaucoma, uveitic glaucoma, and traumatic glaucoma. Although this heterogeneity may be important, as the results apply to a wide patient population, the heterogeneity may obscure any subgroup effect based on type of glaucoma.

For most outcomes specified for this review, data were too sparse to reach meaningful conclusions. Follow-up times varied from one month to five years. The only outcome reported by all five trials was mean IOP 12 months after surgery.

We recognise that each glaucoma drainage device may have different intrinsic IOP-lowering effects and that it may be difficult to differentiate them from the IOP-lowering effects of MMC. However, looking at each trial individually, we observed no evidence of an effect and determined it justifiable to present a combined effect estimate. We observed no statistical heterogeneity (I^2 = 0%).

Quality of the evidence

We assessed the overall certainty of evidence as low, due to unclear risks of bias and imprecision. All included studies were similar in that there was poor reporting of methods, leading to many unknown potential risks of bias. Most of the participants received either MMC or saline placebo in the randomized study eye, but a small number of participants in Duan 2003 had both eyes treated. In these instances, it was unclear whether the two eyes received the same or different interventions.

Potential biases in the review process

We used standard Cochrane methodological procedures to minimize potential biases throughout the process of this review. We reported all available outcomes that had been prespecified in the protocol.

Agreements and disagreements with other studies or reviews

We found one earlier published review on the effectiveness of mitomycin C in aqueous shunt surgery (Yoon 2004), which concluded similar findings to our review that the effects of MMC, and other antfibrotic agents, are unclear in the context of aqueous shunt procedures. Two ongoing RCTs, one using the Ahmed valve implant and the other the Baerveldt tube implant, may provide clearer evidence in updates to this review.

Other smaller case-control studies that have examined MMC as an adjunct to aqueous shunt implantation have concluded certain benefits of intraoperative MMC in certain implants, such as better IOP control at one year post-operation (Perkins 1995) and an increased likelihood of a two to three year period of medical free IOP control in Molteno implant surgery (Perkins 1998) compared to no intraoperative MMC use. Such findings could serve as a rationale for performing more RCTs on the subject in the future to provide stronger evidence for MMC use in aqueous shunts.

AUTHORS' CONCLUSIONS

Implications for practice

Relatively few randomized trials have been published on aqueous shunts and the use of MMC, and the reporting of methodology and data among them is poor. To date, there is no high quality evidence of superiority of MMC use in aqueous shunt surgery over placebo in the reduction of IOP, change in visual acuity, postoperative hypertensive phase, visual field, number of anti-

glaucoma medications used postoperatively, and complications. Further larger-scale RCTs studies are needed to better evaluate the short- or long-term effects of MMC with aqueous shunt surgery.

Implications for research

Additional randomized controlled trials on the use of MMC versus no MMC, or other type of antifibrotic agent, in aqueous shunt surgeries are needed. Also, a smaller treatment effect for one device does not imply it is better or worse unless devices are compared in a single trial. As with other forms of glaucoma, another important issue for future researchers to consider is the outcome definition. IOP represents a surrogate outcome, however, outcomes such as improvement in visual acuity from baseline, visual field progression, or even complication number and type with or without MMC may be more relevant in terms of assessment of benefits of treatment to patients. Perhaps comparing between aqueous shunts with smaller versus bigger surface areas and their outcomes with intraoperative MMC might be useful, or including new shunts in future studies. Additionally, trials may want to stratify based on type of glaucoma in order observe potential subgroup effects.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cantor 1998

Methods	**Study design:** parallel group, randomized controlled trial **Number randomized:** 25 eyes of 25 participants **Exclusions after randomization:** 4 eyes of 4 participants lost to follow-up at 12 months **Number analyzed:** 21 eyes of 21 participants at 12 months **Unit of analysis:** participant (one study eye per participant) **Handling of missing data:** participants lost to follow-up were excluded from the analysis **Sample size calculation:** not reported
Participants	**Country:** USA **Mean age:** 67 years **Gender:** 12 (48%) men and 13 (52%) women **Inclusion criteria:** age 21 years or older; any race; either sex; any lens status; primary open-angle glaucoma; pigment dispersion glaucoma; pseudoexfoliation glaucoma; primary angle-closure glaucoma; neovascular glaucoma; traumatic glaucoma; any secondary open or angle-closure glaucoma; congenital glaucoma; inflammatory glaucoma; any previous ocular surgery other than scleral buckling **Exclusion criteria:** previous aqueous implant shunt placement; previous scleral encircling band placement; pregnancy or lactation **Equivalence of baseline characteristics:** mean IOP at baseline was higher in the Molteno implant with MMC group (41.54 mmHg) than in the control group (34.65 mmHg); 3 black participants in the control group versus none in the MMC group **Diagnoses in participants:** neovascular glaucoma; chronic angle-closure glaucoma; primary open-angle glaucoma; aphakic glaucoma; glaucoma secondary to trauma
Interventions	**MMC group (n = 12):** pressure-ridge, double-plate Molteno implant with topical MMC (0.4 mg/mL applied for 2 minutes with a sponge soaked in the solution) **No MMC group (n = 13):** pressure-ridge, double-plate Molteno implant with BSS stained with gentian violet

Cantor 1998 *(Continued)*

	All participants in both groups received scleral patch grafts; postoperative management included 1% prednisolone acetate and gentamicin four times a day, 1% atropine 2 to 4 times a day and glaucoma medications (except for carbonic anhydrase inhibitors) in the fellow eye, as required.
Outcomes	**Outcomes (primary and secondary outcomes not differentiated):** mean IOP; visual acuity; number of postoperative medications; complications **Length of follow-up:** postoperative week 1, months 1, 3, 6, and 12
Notes	**Study period:** not reported **Trial registration:** not reported **Funding and conflicts of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Masking of participants and personnel (performance bias)	Low risk	Quote: "The surgeon remained masked to which solution was being used." BSS used as placebo
Masking of outcome assessment (detection bias)	Unclear risk	Masking of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Investigators reported 16% of data was missing, with equal duration of follow-up in both groups and no obvious reasons why loss to follow-up should be related to outcome.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record available to compare outcomes
Other bias	Low risk	None identified

Costa 2004

Methods	**Study design:** parallel group, randomized controlled trial **Number randomized:** 60 eyes of 60 participants **Exclusions after randomization:** 28 eyes of 28 participants lost to follow-up at 12 months **Number analyzed:** 32 eyes of 32 participants at 12 months **Unit of analysis:** participant (one study eye per participant) **Handling of missing data:** participants lost to follow-up were excluded from the analysis **Sample size calculation:** not reported
Participants	**Country:** Brazil, Canada, Scotland, USA

Costa 2004 *(Continued)*

	Mean age: 62 years **Gender:** 36 (60%) men and 24 (40%) women **Inclusion criteria:** uncontrolled glaucoma requiring glaucoma drainage device implantation **Exclusion criteria:** younger than 18 years of age; learning difficulties; mental illness; dementia; unconsciousness or severe illness **Equivalence of baseline characteristics:** age, race, lens status, prior glaucoma surgery and IOP similar in the two groups at baseline **Diagnoses in participants:** primary open-angle glaucoma; neovascular glaucoma; congenital glaucoma; traumatic glaucoma; inflammatory and steroid-induced glaucoma; glaucoma following penetrating keratoplasty; aphakic glaucoma
Interventions	**MMC group (n = 34):** Ahmed valve implant with 0.5 mg/mL solution of MMC placed on the epislcera, under the conjunctiva and Tenon's capsule at the site for implant plate for 5 minutes **No MMC group (n = 26):** Ahmed valve implant with topical application of BSS using a soaked sponge on the episclera at site for implant plate for 5 minutes
Outcomes	**Outcomes (primary and secondary outcomes not differentiated):** mean IOP; surgical success, defined as 1) postoperative IOP between 6 and 21 mmHg with or without anti-glaucoma medications or 2) IOP reduction of at least 30% relative to preoperative values; best-corrected visual acuity; number of anti-glaucoma medications; complications **Length of follow-up:** postoperative day 1, weeks 1 and 2, months 1, 3, 6, 12, and 18
Notes	**Study period:** not reported **Trial registration:** not reported **Funding and conflicts of interest:** "The authors have no commercial interest in the products mentioned in the text".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel not reported
Masking of outcome assessment (detection bias)	Unclear risk	Masking of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	28/60 (47%) participants did not complete one year of follow-up.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record available to compare outcomes

Costa 2004 *(Continued)*

Other bias	Low risk	None identified

Duan 2003

Methods	**Study design:** parallel group, randomized controlled trial **Number randomized:** 159 eyes of 154 participants **Exclusions after randomization:** 43 eyes of 38 participants at 12 months **Number analyzed:** 116 eyes of 116 participants at 12 months **Unit of analysis:** eyes **Handling of missing data:** participants lost to follow-up were excluded from the analysis **Sample size calculation:** not reported
Participants	**Country:** China **Mean age:** 50 years **Gender:** 85 (55%) men and 69 (45%) women **Inclusion criteria:** refractory glaucoma (IOP > 25 mmHg on combined pharmacologic therapy) **Exclusion criteria:** none reported **Equivalence of baseline characteristics:** mean IOP at baseline was similar in both intervention groups; the without MMC group had almost twice as many participants with aphakia as in the MMC group; no information on other baseline characteristics was reported **Diagnoses in participants:** neovascular glaucoma; uveitic glaucoma; traumatic glaucoma, primary angle-closure glaucoma; secondary angle-closure glaucoma; juvenile glaucoma; aphakic glaucoma
Interventions	**MMC group (n = 65):** Hunan aqueous device with adjunctive topical application of 0.4 mg/mL MMC with a sponge, applied to the sclera near the equator for 1 to 5 minutes followed by rinsing of extra MMC with balanced salt solution (duration of MMC was determined as follows: minimum duration was 1 minute with addition of 1 minute with each of the following characteristics: age of patient less than 40 years; thick connective tissue; rubeosis iris; IOP > 40 mmHg after combined drug therapy) **No MMC group (n = 94):** Hunan aqueous device with no MMC
Outcomes	**Outcomes (primary and secondary outcomes not differentiated):** mean IOP; surgical success, defined as IOP between 6 and 21 mmHg; best-corrected visual acuity **Length of follow-up:** every 3 months for the first postoperative year and every 6 months thereafter
Notes	**Study period:** July 1995 to July 2001 **Trial registration:** not reported **Funding and conflicts of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported

Duan 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel not reported
Masking of outcome assessment (detection bias)	Unclear risk	Masking of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	38/154 (25%) participants did not complete one year of follow-up.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record available to compare outcomes
Other bias	Low risk	None identified

Kalenak 1996

Methods	**Study design:** parallel group, randomized controlled trial **Number randomized:** 25 eyes of 25 participants **Exclusions after randomization:** none reported **Number analyzed:** 25 eyes of 25 participants **Unit of analysis:** participant (one study eye per participant) **Handling of missing data:** none reported **Sample size calculation:** not reported
Participants	**Country:** USA **Mean age:** not reported **Gender:** not reported **Inclusion criteria:** glaucoma with inadequately controlled IOP; at least one previous glaucoma filtering operation **Exclusion criteria:** neovascular glaucoma **Equivalence of baseline characteristics:** not reported **Diagnoses in participants:** non-neovascular glaucoma
Interventions	**MMC group (n = 12):** single-plate Molteno implant with MMC (0.2 mg/mL) **No MMC group (n = 13):** single-plate Molteno implant with placebo for 5 minutes
Outcomes	**Outcomes (primary and secondary outcomes not differentiated):** mean IOP; surgical success, defined as IOP between 6 and 21 mmHg **Length of follow-up:** "6 months or more, or to a defined endpoint"

Kalenak 1996 *(Continued)*

Notes	**Study period:** not reported **Trial registration:** not reported **Funding and conflicts of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel not reported
Masking of outcome assessment (detection bias)	Unclear risk	Masking of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data not reported
Selective reporting (reporting bias)	High risk	No full-length paper published more than 20 years after presenting the trial at a conference
Other bias	Low risk	None identified

Sayyad 1995

Methods	**Study design:** parallel group, randomized controlled trial **Number randomized:** 64 eyes (number of participants not reported) **Exclusions after randomization:** none reported **Number analyzed:** 64 eyes **Unit of analysis:** not reported **Handling of missing data:** none reported **Sample size calculation:** not reported
Participants	**Country:** Saudi Arabia **Mean age:** not reported **Gender:** not reported **Inclusion criteria:** complicated glaucoma **Exclusion criteria:** not reported **Equivalence of baseline characteristics:** not reported

Sayyad 1995 *(Continued)*

	Diagnoses in participants: complicated glaucoma
Interventions	**MMC group (n not reported):** single-plate Molteno implant with MMC and trabeculectomy **No MMC group (n not reported):** single-plate Molteno implant only In all participants in both groups the Molteno tube was ligated temporarily
Outcomes	**Outcomes (primary and secondary outcomes not differentiated):** mean IOP **Length of follow-up:** postoperative day 14, months 3, and 12
Notes	**Study period:** not reported **Trial registration:** not reported **Funding and conflicts of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel not reported
Masking of outcome assessment (detection bias)	Unclear risk	Masking of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data not reported
Selective reporting (reporting bias)	High risk	No full-length paper published more than 20 years after presenting the trial at a conference
Other bias	Low risk	None identified

BSS: balanced salt solution
IOP: intraocular pressure
mg/mL: milligrams per milliliter
MMC: mitomycin C
mmHg: millimeter of mercury

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chua 2002	Randomization not specified (reported as a conference abstract only); compared Ahmed aqueous shunt surgery with versus without intra-Tenon injection of MMC

Study	Reason for exclusion
Cillino 2008	No aqueous shunt; randomized trial that compared four groups: trabeculectomy, trabeculectomy with MMC, trabeculectomy with expanded polytetrafluoroethylene, and trabeculectomy with both MMC and expanded polytetrafluoroethylene
Kurnaz 2005	Not a randomized trial; cohort study that compared effects of MMC versus no MMC in Ahmed aqueous shunt surgery
Mahdy 2011	Ineligible comparator; compared Ahmed aqueous shunt surgery with MMC versus bevacizumab for pediatric glaucoma
Yazdani 2015	Ineligible comparator; compared Ahmed aqueous shunt surgery with MMC versus amniotic membrane transplant

MMC: mitomycin-C

Characteristics of ongoing studies *[ordered by study ID]*

IRCT2015101024459N1

Trial name or title	Evaluation of the efficacy of Ahmed Glaucoma Valve Implantation with and without Mitomycin C during surgery in patients with glaucoma
Methods	**Study design:** parallel group, randomized controlled trial **Planned enrolment:** 60 participants **Unit of analysis:** participant (one study eye per participant) **Sample size calculation:** not reported
Participants	**Country:** Iran **Inclusion criteria:** 18 years of age or older; uncontrolled glaucoma; candidate for aqueous shunt surgery **Exclusion criteria:** active iris neovascularization, anterior staphyloma, breastfeeding, pregnancy, previous shunt surgery, corneal lesions that prevent IOP measurement
Interventions	**MMC group:** 1-stage Ahmed valve implant with MMC (0.02%) **No MMC group:** Ahmed valve implant with placebo (balanced salt solution)
Outcomes	**Primary outcome:** IOP **Secondary outcomes:** tube-corneal contact, number of antiglaucoma medications, hyphema, retraction of tube from anterior chamber, tube/implant exposure, flat chamber/transient hypotony, choroidal effusion, blocked tube **Length of follow-up:** postoperative day 1, week 1, and months 1, 3, 6, and 12
Starting date	November 2015
Contact information	Dr. Ghasem Fakhraee Farabi Eye Hospital Tehran University of Medical Sciences

IRCT2015101024459N1 *(Continued)*

Notes	**Conflicts of interest:** not reported

NCT02989207

Trial name or title	Surgical approaches in treating uncontrolled glaucoma in black African and African-Caribbeans (PEACE)
Methods	**Study design:** parallel group, randomized controlled trial **Planned enrolment:** 60 participants **Unit of analysis:** not reported **Sample size calculation:** not reported
Participants	**Country:** UK **Inclusion criteria:** 18 to 85 years of age, black African Caribbean or African (self-reported), uncontrolled glaucoma (IOP between 18 and 40 mmHg) **Exclusion criteria:** breastfeeding, pregnancy, previous incisional surgery (except for phacoemulsification or minimally invasive glaucoma shunt surgery), no light perception vision, active diabetic retinopathy, secondary glaucoma, unwilling to discontinue contact lens use post-surgery, conjunctival scarring (precluding superior trabeculectomy), functionally significant cataract likely to require surgery within 6 months of glaucoma surgery, previous complicated cataract surgery in study eye, need for glaucoma surgery with other ocular procedures, iris neovascularization or proliferative retinopathy, iridocorneal endothelial syndrome, epithelial or fibrous downgrowth, chronic or recurrent uveitis, steroid-induced glaucoma, severe posterior blepharitis
Interventions	**MMC group:** Baerveldt tube surgery with MMC (0.02%) **No MMC group:** Baerveldt tube surgery without MMC **Other group:** trabeculectomy with MMC
Outcomes	**Primary outcome:** the number of potential participants enrolled over a set time **Secondary outcomes:** success rate, defined as eyes that have not failed and are not on supplemental medical therapy; failure rate, defined as IOP > 21 mmHg or not reduced by 20% below baseline on two consecutive follow-up visits, additional glaucoma surgery, loss of vision, or IOP < 5 mmHg on two consecutive follow-up visits; complication rate; the number of extra unscheduled clinic visits and unplanned procedures; loss to follow-up rate; response rates to the self-report **Length of follow-up:** up to 6 months
Starting date	August 2016
Contact information	Sheng Lim, MD; Stephanie Jones Guy's and St Thomas' NHS Foundation Trust
Notes	**Conflicts of interest:** not reported

IOP: intraocular pressure
MMC: mitomycin C

DATA AND ANALYSES

Comparison 1. Mitomycin C versus placebo during aqueous shunt surgery

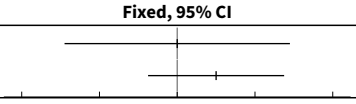
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean intraocular pressure at 4 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Mean intraocular pressure at 12 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Mean intraocular pressure at 6 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Mean intraocular pressure at 12 months	3	78	Mean Difference (IV, Fixed, 95% CI)	0.12 [-2.16, 2.41]
5 Mean number of antiglaucoma medications at 12 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Proportion of participants with adverse event	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Choroidal effusion	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Corneal edema	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Flat anterior chamber	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Retinal detachment	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Mitomycin C versus placebo during aqueous shunt surgery, Outcome 1 Mean intraocular pressure at 4 weeks.

Study or subgroup	Favors mitomycin C		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Cantor 1998	12	15.8 (11.8)	13	18.5 (10.1)		-2.7[-11.34,5.94]
Costa 2004	34	17.5 (8.3)	25	20 (9.5)		-2.5[-7.15,2.15]

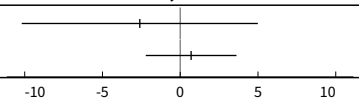
Analysis 1.2. Comparison 1 Mitomycin C versus placebo during aqueous shunt surgery, Outcome 2 Mean intraocular pressure at 12 weeks.

Study or subgroup	Favors mitomycin C		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Cantor 1998	12	18.8 (8)	12	18.8 (10)		0[-7.25,7.25]
Costa 2004	31	20 (9.5)	23	17.5 (6.9)		2.5[-1.87,6.87]



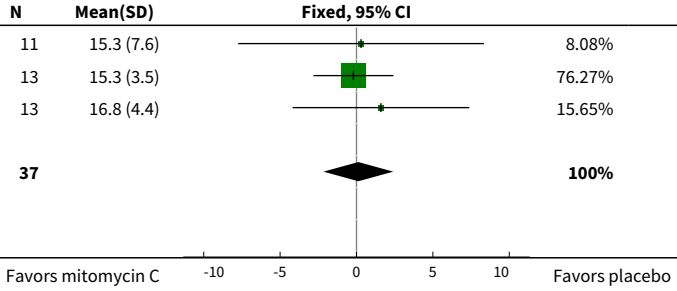
Analysis 1.3. Comparison 1 Mitomycin C versus placebo during aqueous shunt surgery, Outcome 3 Mean intraocular pressure at 6 months.

Study or subgroup	Favors mitomycin C		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Cantor 1998	12	17.7 (4.9)	13	20.3 (13)		-2.6[-10.19,4.99]
Costa 2004	28	16.6 (6.7)	20	15.9 (3.5)		0.7[-2.22,3.62]



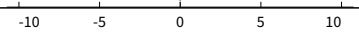
Analysis 1.4. Comparison 1 Mitomycin C versus placebo during aqueous shunt surgery, Outcome 4 Mean intraocular pressure at 12 months.

Study or subgroup	Mitomycin C		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Cantor 1998	10	15.6 (10.8)	11	15.3 (7.6)		8.08%	0.3[-7.75,8.35]
Costa 2004	19	15.1 (4)	13	15.3 (3.5)		76.27%	-0.2[-2.82,2.42]
Kalenak 1996	12	18.4 (9.3)	13	16.8 (4.4)		15.65%	1.6[-4.18,7.38]
Total ***	**41**		**37**			**100%**	**0.12[-2.16,2.41]**
Heterogeneity: Tau^2=0; Chi^2=0.31, df=2(P=0.86); I^2=0%							
Test for overall effect: Z=0.1(P=0.92)							



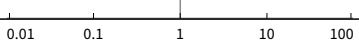
Analysis 1.5. Comparison 1 Mitomycin C versus placebo during aqueous shunt surgery, Outcome 5 Mean number of antiglaucoma medications at 12 months.

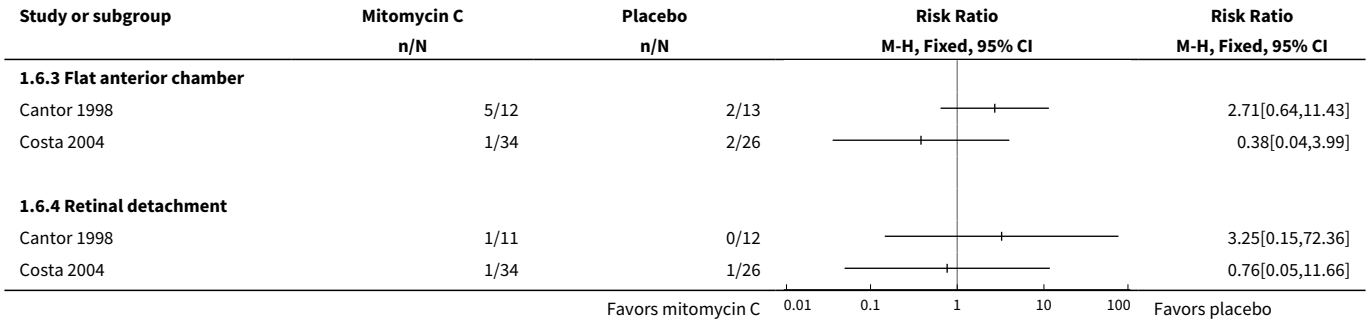
Study or subgroup	Mitomycin C		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Cantor 1998	10	0.8 (0.8)	11	1.1 (0.9)		-0.3[-1.03,0.43]
Costa 2004	19	1.3 (1)	13	1.3 (0.8)		0[-0.63,0.63]



Analysis 1.6. Comparison 1 Mitomycin C versus placebo during aqueous shunt surgery, Outcome 6 Proportion of participants with adverse event.

Study or subgroup	Mitomycin C	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.6.1 Choroidal effusion				
Cantor 1998	1/12	3/13		0.36[0.04,3.02]
Costa 2004	6/34	5/26		0.92[0.31,2.68]
1.6.2 Corneal edema				
Cantor 1998	4/12	2/13		2.17[0.48,9.76]
Costa 2004	3/34	1/26		2.29[0.25,20.8]





APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma] explode all trees
#2 MeSH descriptor: [Ocular Hypertension] explode all trees
#3 MeSH descriptor: [Intraocular Pressure] explode all trees
#4 glaucoma*
#5 ((intra*ocular or ocular*) near/3 (hypertension* or tension* or pressur*))
#6 IOP
#7 MeSH descriptor: [Filtering Surgery] explode all trees
#8 MeSH descriptor: [Cataract Extraction] explode all trees
#9 (cataract* near/3 (extract* or surg* or operat* or remov*))
#10 {or #1-#9}
#11 MeSH descriptor: [Glaucoma Drainage Implants] explode all trees
#12 (Baerveldt* or Krupin* or Ahmed* or Molteno* or Schocket* or Joseph* or Optimed* or White or Hunan*)
#13 (Devic* or implant* or shunt* or valve* or tube* or drain* or seton*)
#14 {or #11-#13}
#15 MeSH descriptor: [Mitomycin] explode all trees
#16 (Mitomycin* or NSC-26980 or NSC 26980 or NSC26980 or Mutamycin or Ametycine or Mitocin-C or MitocinC or mytomycin* or mitomicin* or mytomicin* or MMC)
#17 MeSH descriptor: [Mitomycins] explode all trees
#18 #17 Publication Year from 1966 to 1991
#19 MeSH descriptor: [Antimetabolites] this term only
#20 MeSH descriptor: [Antimetabolites, Antineoplastic] explode all trees
#21 MeSH descriptor: [Nucleic Acid Synthesis Inhibitors] explode all trees
#22 (Antimetabolit* or anti-metabolit*)
#23 (Antifibrotic* or anti-fibrotic*)
#24 {or #15-#16, #18-#23}
#25 #10 and #14 and #24

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Glaucoma/
13. exp ocular hypertension/

14. exp intraocular pressure/
15. glaucoma*.tw.
16. ((intra?ocular or ocular*) adj3 (hypertension* or tension* or pressur*)).tw.
17. IOP.tw.
18. exp filtering surgery/
19. exp Cataract Extraction/
20. (cataract* adj3 (extract* or surg* or operat* or remov*)).tw.
21. or/12-20
22. exp Glaucoma Drainage Implants/
23. (Baerveldt* or Krupin* or Ahmed* or Molteno* or Schocket* or Joseph* or Optimed* or White or Hunan*).tw.
24. (glaucom* and (Devic* or implant* or shunt* or valve* or tube* or drain* or seton*)).tw.
25. or/22-24
26. exp Mitomycin/
27. (Mitomycin* or NSC-26980 or NSC 26980 or NSC26980 or Mutamycin or Ametycine or Mitocin-C or MitocinC or mytomycin* or mitomicin* or mytomicin* or MMC).tw.
28. exp Mitomycins/
29. limit 28 to yr="1966 - 1991"
30. antimetabolites/
31. exp Antimetabolites, Antineoplastic/
32. exp Nucleic Acid Synthesis Inhibitors/
33. (Antimetabolit* or anti-metabolit*).tw.
34. (Antifibrotic* or anti-fibrotic*).tw.
35. or/26-27,29-34
36. 21 and 25 and 35
37. 36 and 11

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31

#33 'glaucoma'/exp
#34 'intraocular pressure'/exp
#35 'intraocular pressure abnormality'/de
#36 'ocular ischemic syndrome'/exp
#37 glaucom*:ab,ti
#38 ((intra*ocular OR ocular*) NEAR/3 (hypertension* OR tension* OR pressur*)):ab,ti
#39 iop:ab,ti
#40 'filtering operation'/exp
#41 'cataract extraction'/exp
#42 (cataract* NEAR/3 (extract* OR surg* OR operat* OR remov*)):ab,ti
#43 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
#44 'glaucoma drainage implant'/exp
#45 baerveldt*:ab,ti OR krupin*:ab,ti OR ahmed*:ab,ti OR molteno*:ab,ti OR schocket*:ab,ti OR joseph*:ab,ti OR optimed*:ab,ti OR white:ab,ti OR hunan*:ab,ti
#46 glaucom*:ab,ti AND (devic*:ab,ti OR implant*:ab,ti OR shunt*:ab,ti OR valve*:ab,ti OR tube*:ab,ti OR drain*:ab,ti OR seton*:ab,ti)
#47 #44 OR #45 OR #46
#48 'mitomycin'/exp
#49 mitomycin*:ab,ti OR 'nsc 26980':ab,ti OR nsc26980:ab,ti OR mutamycin:ab,ti OR ametycine:ab,ti OR 'mitocin c':ab,ti OR mitocinc:ab,ti OR mytomycin*:ab,ti OR mitomicin*:ab,ti OR mytomicin*:ab,ti OR mmc:ab,ti OR datisan:ab,ti OR metomit:ab,ti OR mitocyna:ab,ti OR mitosol:ab,ti OR mixandex:ab,ti OR mytocine:ab,ti OR mytozytrex:ab,ti OR vetio:ab,ti OR '1404 00 8':ab,ti
#50 'antimetabolite'/de
#51 'antineoplastic antimetabolite'/exp
#52 'nucleic acid synthesis inhibitor'/exp
#53 antimetabolit*:ab,ti OR (anti NEAR/1 metabolit*):ab,ti
#54 antifibrotic*:ab,ti OR (anti NEAR/1 fibrotic*):ab,ti
#55 #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54
#56 #43 AND #47 AND #55
#57 #32 AND #56

Appendix 4. PubMed search strategy

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
#2 Glaucoma*[tw] NOT MEDLINE[sb]
#3 ((intraocular[tw] OR ocular*[tw]) AND (hypertension*[tw] OR tension*[tw] OR pressur*[tw])) NOT MEDLINE[sb]
#4 IOP[tw] NOT MEDLINE[sb]
#5 (cataract*[tw] AND (extract*[tw] OR surg*[tw] OR operat*[tw] OR remov*[tw])) NOT MEDLINE[sb]
#6 #2 OR #3 OR #4 OR #5
#7 (Baerveldt*[tw] OR Krupin*[tw] OR Molteno*[tw] OR Molteno*[tw] OR Schocket*[tw] OR Joseph*[tw] OR Optimed*[tw] OR White[tw] OR Hunan*[tw]) NOT MEDLINE[sb]
#8 glaucom*[tw] AND (Devic*[tw] OR implant*[tw] OR shunt*[tw] OR valve*[tw] OR tube*[tw] OR drain*[tw] OR seton*[tw]) NOT MEDLINE[sb]
#9 #7 OR #8
#10 (Mitomycin*[tw] OR NSC-26980[tw] OR "NSC 26980"[tw] OR NSC26980[tw] OR Mutamycin[tw] OR Ametycine[tw] OR Mitocin-C[tw] OR MitocinC[tw] OR mytomycin*[tw] OR mitomicin*[tw] OR mytomicin*[tw] OR MMC[tw]) NOT MEDLINE[sb]
#11 (Antifibrotic*[tw] OR anti-fibrotic*[tw]) NOT MEDLINE[sb]
#12 #10 OR #11
#13 #6 AND #9 AND #12
#14 #1 AND #13

Appendix 5. LILACS search strategy

(MH:C11.525$ OR glaucoma$ OR "Ocular Hypertension" OR "Hipertensión Ocular" OR "Hipertensão Ocular" OR MH:G14.440$ OR ((intraocular OR "intra-ocular" OR ocular$) AND (hypertension$ OR tension$ OR pressur$)) OR "Presión Intraocular" OR "Pressão Intraocular" OR IOP OR MH:E04.540.450$ OR MH:E04.540.825.249$ OR (cataract$ AND (extract$ OR surg$ OR operat$ OR remov$))) AND (MH:E07.695.250$ OR "Implantes de Drenaje de Glaucoma" OR "Implantes para Drenagem de Glaucoma" OR Baerveldt$ OR Krupin$ OR Ahmed$ OR Molteno$ OR Schocket$ OR Joseph$ OR Optimed$ OR White OR Hunan$ OR Devic$ OR implant$ OR shunt$ OR valve$ OR tube$ OR drain$ OR seton$) AND (MH:D02.806.400.249.350$ OR MH:D03.383.097.500.350$ OR MH:D03.438.473.412.249.350$ OR Mitomycin $ OR NSC-26980 OR "NSC 26980" OR NSC26980 OR Mutamycin OR Ametycine OR Mitocin-C OR MitocinC OR mytomycin$ OR mitomicin$ OR mytomicin$ OR MMC OR MH:D27.505.519.186 OR MH:D27.888.569.042 OR MH:D27.505.519.186.144$ OR MH:D27.505.954.248.144$ OR MH:D27.888.569.042.030$ OR MH:D27.505.519.389.675$ OR Antimetabolit$ or anti-metabolit$ OR Antifibrotic$ or anti-fibrotic$)

Appendix 6. ClinicalTrials.gov search strategy

(glaucoma OR hypertension OR intraocular pressure) AND (device OR implant OR implants OR shunt OR valve OR tube OR drain OR drainage OR seton OR Baerveldt OR Krupin OR Ahmed OR Molteno OR Schocket OR Joseph OR Optimed OR White OR Hunan) AND (Mitomycin OR Mytomycin OR MMC OR Antimetabolite OR Antimetabolites)

Appendix 7. WHO ICTRP search strategy

Glaucoma AND Mitomycin OR Glaucoma AND Mytomycin OR Glaucoma AND MMC OR Glaucoma AND Antimetabolite OR Glaucoma AND Antimetabolites OR hypertension AND Mitomycin OR hypertension AND Mytomycin OR hypertension AND MMC OR hypertension AND Antimetabolite OR hypertension AND Antimetabolites OR intraocular pressure AND Mitomycin OR intraocular pressure AND Mytomycin OR intraocular pressure AND MMC OR intraocular pressure AND Antimetabolite OR intraocular pressure AND Antimetabolites

CONTRIBUTIONS OF AUTHORS

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Organization and retrieval of papers: CEV US Satellite
Appraising the quality of papers: VHXF, CEV US Satellite
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Entering data into RevMan: VHXF
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added methods for the 'Summary of findings' table and GRADE assessment, which both were incorporated in Cochrane reviews after the publication of the protocol (Foo 2015). We did not conduct subgroup analysis or sensitivity analysis due to insufficient data.

INDEX TERMS

Medical Subject Headings (MeSH)

*Glaucoma Drainage Implants; Glaucoma [surgery] [*therapy]; Mitomycin [*therapeutic use]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Humans